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(54) Title: COVALENT CONJUGATES OF BIOLOGICALLY-ACTIVE COMPOUNDS WITH AMINO ACIDS AND AMINO ACID DERIVATIVES FOR TARGETING TO PHYSIOLOGICALLY-PROTECTED SITES

(57) Abstract: This invention herein describes a method of facilitating the entry of drugs into cells and tissues at physiologically protected sites at pharmacokinetically useful levels and also a method of targeting drugs to physiologically protected sites *in vivo*. Also provided are drug conjugates with an amino acid or derivative thereof for facilitating such targeted drug delivery. The conjugates and methods of this invention provide an advance over other drug targeting methods known in the prior art, because the invention provides drug concentrations in such physiologically protected sites that can reach therapeutically-effective levels after administration of systemic levels much lower than are currently administered to achieve a therapeutic dose. This technology is appropriate for use with psychotropic, neurotropic, neurological, antibiotic, antibacterial, antimycotic, antiviral, antiproliferative or antineoplastic drugs, agents and conjugates, for rapid and efficient introduction of such agents across, e.g., the blood-brain barrier. Further, the invention provides means for retention and prolonged enzymatic release of such drugs, agents and conjugates comprising the conjugates of the invention, in the brain and central nervous system and other physiologically-protected sites.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/35106

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/00, 38/00, 31/135, 31/685, 9/127

US CL : 514/2, 78, 863, 649; 424/450

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/2, 78, 863, 649; 424/450

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
USPATFULL

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 5,149,794 A (YATVIN et al.) 22 September 1992 (22.09.1992), Fig. 1-8, Example 1-8, claims 1-10.	1-19
X	US 5,543,389 A (YATVIN et al.) 6 August 1996 (06.08.1996), Fig. 1, Example 1, claims 1-36.	1-19
X	US 5,827,819 A (YATVIN et al.) 27 October 1998 (27.10.1998), Fig. 1-6, Examples 1-6, claims 1-12.	1-19

☐ Further documents are listed in the continuation of Box C.

☐ See patent family annex.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier application or patent published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "&" document member of the same patent family

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Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This international report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claim Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☐ Claim Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☒ Claim Nos.: 20-33
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐
☐

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.